Biolife 5(3):314-320
AN INTERNATIONAL QUARTERLY JOURNAL OF BIOLOGY & LIFE SCIENCES
ISSN (online): 2320-4257
www.biolifejournals.com
BIOLIFE CASE REPORT

Transcranial doppler as an early predictor of Delerium in septic patients and its correlation with Jagular Venous Oxygen saturation

M. Omar Elghonemi[1], M. Hosni[2], A. Safwat[3], M. Elsakaan[4]

[1,2] *Department of Critical care, University of Cairo, Egypt*
[3] *Department of Neurology, University of Ain Shams, Egypt*
[4] *Department of Radiology, Students Hospital of Cairo, University, Egypt*

Email: Elghonemi@yahoo.com

ABSTRACT

Background: Impairment of cerebrovascular autoregulation is considered one of the most important mechanisms leading to cerebral hypo- or hyperperfusion in haemodynamically unstable septic patients. That may lead to Sepsis-associated delirium (SAD) which increases morbidity and mortality. Objective: To investigate the ability of Trans cranial Doppler (TCD) for prediction of delirium in septic patient and its relationship with jagular venous oxygen saturation (JVo2) levels.
Method: On the first day we used a 3-MHz Tran's cranial Doppler probe to measure the Blood velocity and Pulsatility index in the middle cerebral artery (VMCA) TCD was then repeated daily for 3 consecutive days. Simultaneously we measured r jugular venous oxygen saturation (JVO2) on the same side of the highest VMCA. Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was done for each patient once per day throughout ICU stay and after 6 hours after stoppage of sedation in sedated patient.
Results: Out of 159 patients, 91 developed delirium. APACHE score was higher in the delirium group. Patients who developed delirium had significantly longer ICU LOS 13.9 day's vs 7.8 Delirium group had lower mean MCA velocity and higher pulsatility index at all times .Positive correlation was observed between Jvo2 and VMCA on day 2 (r=0.8), and on day 3 (r=0.69). There was a negative correlation between PI and JVo2 on day 2(r= -0.5) and day 3(r=-0.57). Roc curve analyses the ability to detect delirium with a cut off value for Jvo2 measured at day 3(Jvo2 3) of 53.5 % (sensitivity 100%, specificity 100%, P <0.05), and a cut off value for the PI at day 3 (PI3) of 1.2. (AUC= 0.88, CI 95%, 0.83-0.9 P <0.05vsensitivity 70%, specificity 100%).
Conclusion: Changes in TCD findings together with JVo2 levels are associated with the development of delirium in septic patients.

Key words: Transcranial Doppler, Sepsis, Delirium, Sepsis, Jugular venous oxygen saturation.

INTRODUCTION

Among the multi-organ dysfunctions present in sepsis, brain dysfunction is one of the 1st clinical symptoms. In nearly 70% sepsis patients, brain dysfunction may develop as sepsis associated delirium [1, 2], followed by focal deficits or seizures [3].The main pathophysiology of severe sepsis and septic shock are hypo-tension, misdistribution of regional blood flow, and tissue hypo-perfusion. Theoretically there is an association between cerebral perfusion and brain dysfunction in sepsis. On the contrary clinical and experimental data show inconsistent results to this theory.

How to Site This Article:
M. Omar Elghonemi, M. Hosni, A. Safwat, M. Elsakaan. (2017). Transcranial doppler as an early predictor of Delerium in septic patients and its correlation with Jagular Venous Oxygen saturation. *Biolife*. 5(3), pp 314-320.

DOI: 10.5281/zenodo.7364773
Received: 3 July 2017;
Accepted; 18 August 2017;
Available online : 1 September 2017

Despite the findings of an experimental sepsis model which elaborates the existence of microcirculatory dysfunction and dissociation between cerebral cells' needs and perfusion at several cerebral areas [4, 5], in humans this dysfunction isn't widely assessed. Also the evaluation attempts of cerebral blood flow or microcirculation during sepsis remain very few to be considered applicable methods of evaluation [6, 7, 8]. One technique of evaluation is the Transcranial Doppler (TCD) which can be used to evaluate cerebral perfusion in everyday clinical practice. TCD is used to assess indirect cerebral microcirculation by testing cerebral auto regulation in response to several stimulations [9 - 14].An adverse relation is present between the densities of perfused microvessels cerebrovascular resistance. The pulsatility index (PI), as (an indicator of cerebrovascular resistance) has been found to be higher in septic patients than [15] non-septic critically ill patients.[16]

We performed this study to investigate the ability of Transcranial Doppler (TCD) to predict delirium in septic patient and its relationship to JVo2 levels.

MATERIAL AND METHODS

A prospective, observational study was carried out in the medical intensive care unit during the period of January 2015 to January 2016. Patients were admitted as soon as they were diagnosed with sepsis. Sepsis and septic shock were defined according to standard international definition.[17]We excluded patients who were: under 18 years old, suffering from any acute or chronic neurological disease (cerebrovascular disorders, traumatic brain injury, seizure disorders, neoplasm,and CNS infections), known intoxications, significant carotid stenosis, and patients who need continuous sedation for whom assessment will not be suitable. All baseline demographic data were collected together with routine blood labs and cultures. Source and length of sepsis were noted - when possible -and APACHE II was computed to assess severity.

On the first day we used a 3-MHz Transcranial doppler (TCD) probe to measure the Blood velocity in the middle cerebral artery (VMCA) on both sides and the higher value was registered. TCD was then repeated daily on the same side for 3 consecutive days (hence each patient had 3 readings at day 1, day 2 and day3). Pulsatility index was calculated (PI = velocity systolic-velocity diastolic/mean velocity)[18] .Simultaneously we sampled the Jugular vein for jugular venous oxygen saturation (JVO2) on the same side of the highest VMCA.

CAM-ICU was done for each patient once per day throughout ICU stay. If patients were sedated then CAM-ICU was done 6 hours after stoppage of sedation.[19].

Statistical analysis was performed with SPSS software (SPSS Inc., Chicago, IL). A Kolomogorov-Smirnov test was used to verify the normality of distribution of continuous variables. Student's t test was used for continuous variables. Categorical variables were compared by Fisher's exact test. Pearson's correlation was applied to evaluate the relationships between VMCA, PI, RI, and pCO2 or MAP and between VMCA and CBFi. Statistical significance was defined as $p < 0.05$.

RESULTS

We studied 159 patients admitted to the ICU with sepsis. Tables 1, 2 and 3 show the baseline characters of the patients.

Table-1. General characters of the patients

Characters	Patients (n=159)
Age	52.2 ± 7.4
Sex (female)	76
Diabetes	77
HTN	74
APACHE	29.2 ± 8.7
LOS (days)	10.3 ± 5.6
Mortality	74

Table-2. Cause of sepsis and causative organism

Cause	Patients (n=159)
Pneumonia	63
UTI	44
skin soft tissue	28
other** abd sinus blood	24
Gram +ve	58
Gram -ve	72
fungal	14
Anaerobic	11
none	4

Table-3. Values during admission

laboratory & imaging values	Patients (n=159)
CRP	187.9
MAP 1	73.8
Sat1	96.2
Co21	45.1
JVO21	64.4
VMCA 1	53.2
PI 1	1.15

The mean APACHE II was 29.2 and the mean ICU stay was 10.3 days. The main two causes of sepsis were pneumonia and urinary tract infections, followed by skin & soft tissue infections, and other sources (abdominal, catheter related and sinusitis). Gram –ve organisms were the most prevalent in the study group followed by gram +ve, fungal and anerobic organisms. Out of the 159 patients, 74 died during the ICU stay.

91 patients developed delirium (Positive CAMICU) while 68 patients did not develop delirium. Tables 4 & 5 show baseline characters once sepsis was diagnosed.

Table-4. Patients characters in delirium and non-delerium groups

	No Delirium (n = 68)	Delirium (n = 91)	P value
Age	51.3	53.4	P=0.07
Sex (female)	42	34	P=0.63
APACHE	22.5	38	P=0.00
LOS	7.8	13.9	P=0.00

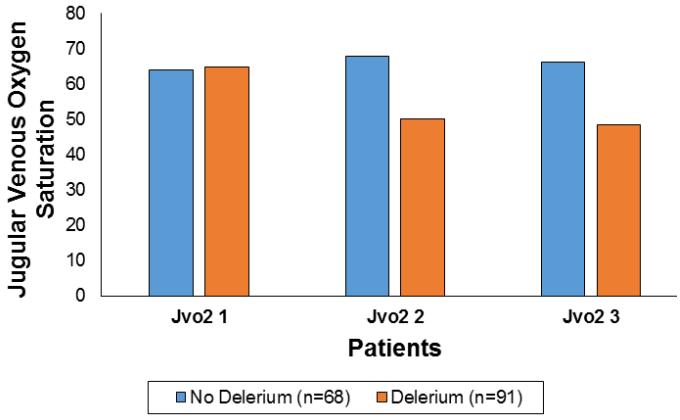
Table-5. Hemodynamics of delirium versus non-delerium groups

	No Delirium (n=68)	Delirium (n=91)	P value
MAP1	76.3	70.5	P=0.00
MAP2	79.2	74.9	P=0.00
MAP3	79.6	75.7	P=0.001
SAT1	90.3	96.1	P=0.5
SAT2	95.4	97	P=0.00
SAT3	94.9	93.6	P=0.003
Jvo2 1	64	64.9	P=0.27
Jvo2 2	68	50.2	P=0.00
Jvo2 3	66.2	48.5	P=0.00

APACHE II score was higher in the delirium group. Patients who developed delirium had significantly longer ICU LOS. MAP was significantly lower in patients who developed delirium. Interestingly Sao2 was found higher in patients who developed delirium at day 1 and 2. JVo2 was significantly lower in the delirium group at day 2 and 3.

JVO2 measured on day 2 and s day 3 was found lower in patients who developed delirium. [Fig-1]

Fig-1. Jugular venous oxygen saturation in delirium and non- delirium patients



.

Table-6 shows Transcranial Doppler findings in the study group. Patients who developed delirium had lower mean MCA velocity (VMCA) [fig-2] and higher pulsatility index at all times [fig-3].

Table-6. TCD results in delirium versus non-delerium groups

	No Delerium (n=68)	Delerium (n=91)	P value
VMCA1	59.7	44.5	P=0.00
VMCA2	60.6	36.1	P=0.00
VMCA3	59.3	39.8	P=0.00
PI1	1.13	1.18	P=0.007
PI2	1.21	1.43	P=0.00
PI3	1.2	1.37	P=0.00

Fig-2. Mean velocity of MCA (VMCA) in delirium and non-delirium patients

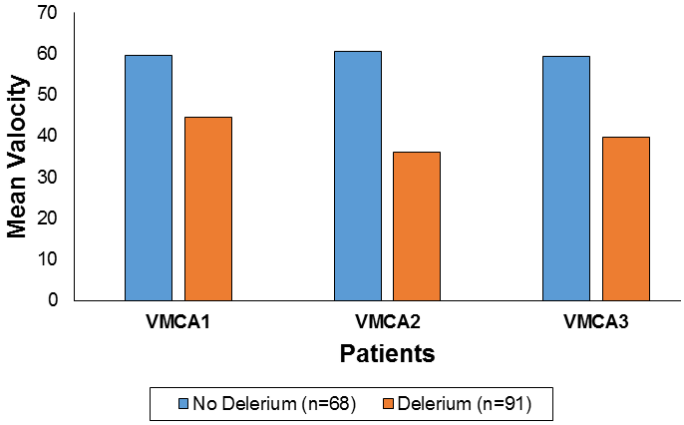
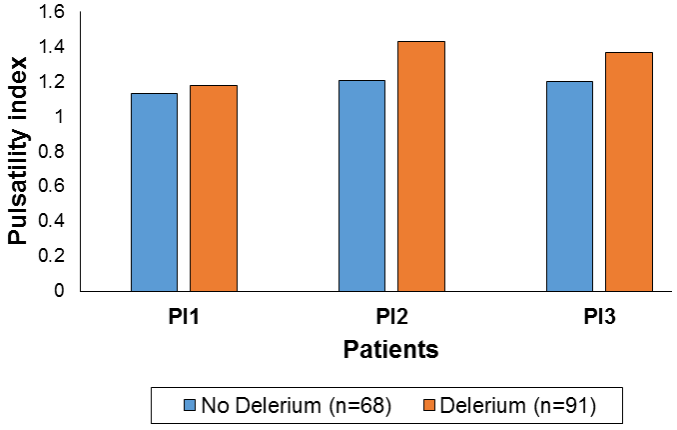


Fig-3. Pulsatility index for delirium and non-delirium patients



Correlations:-

We detected a strong positive correlation between Jvo2 and VMCA on day 2 (r=0.8), and on day 3 (r=0.69, p=0.00) (fig-4 & 5). A negative correlation was observed between PI and JVo2 on day 2(r=-0.5,p=0.00) and day 3(r=-o.57) (fig-6 & 7)

Fig-4. Correlation between JVO2 and VMCA on day 2

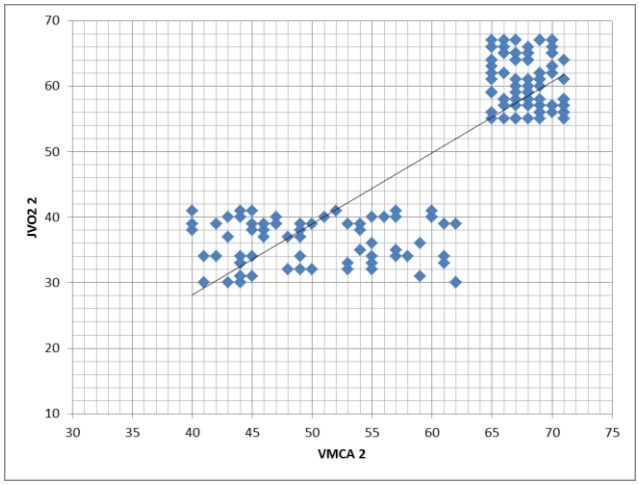


Fig-5. Correlation between JVO2 and VMCA on day 3

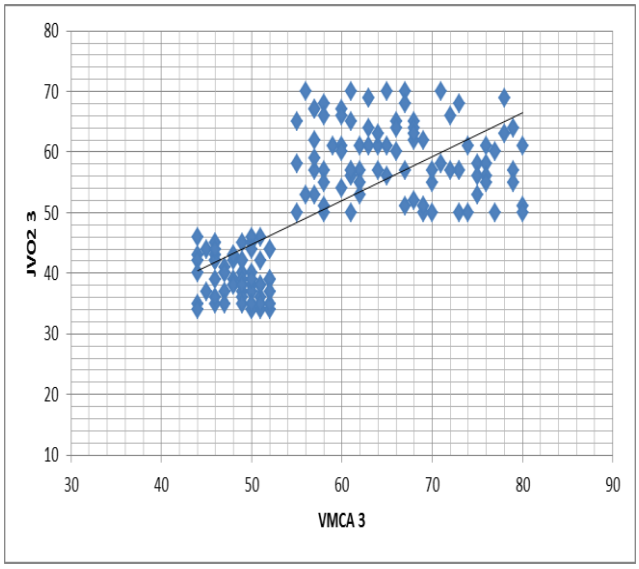


Fig-6. Correlation between JVO2 and PI on day 2

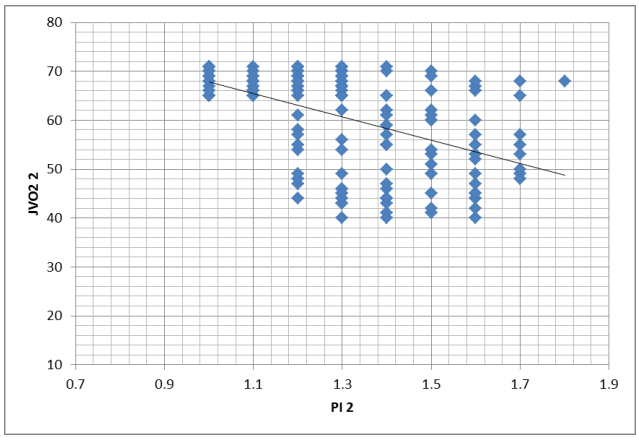


Fig-7. Correlation between JVO2 and PI on day 3

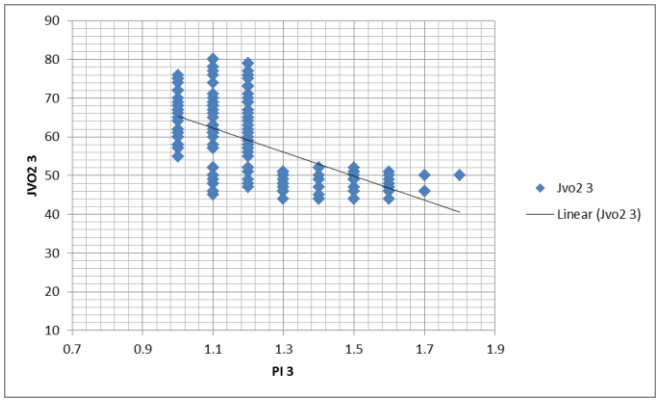


Fig-8. ROC curve for Jvo2

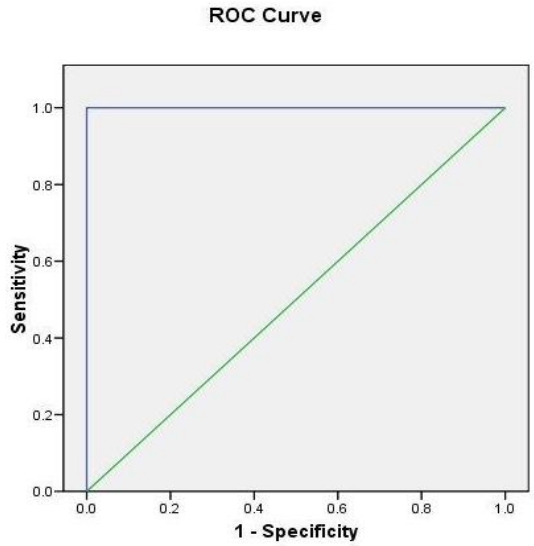
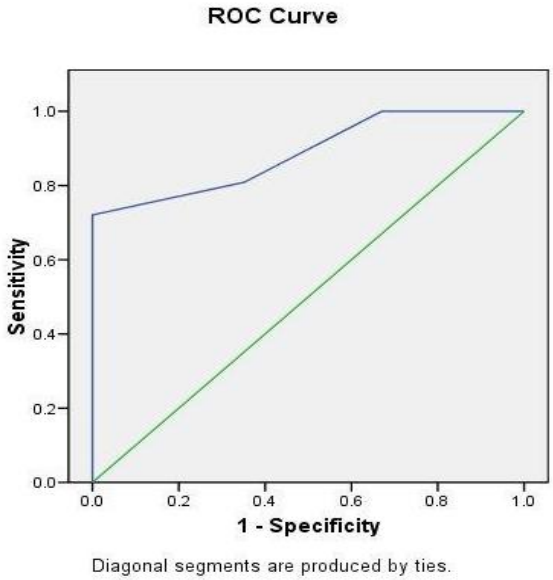


Fig-9. ROC curve for PI



ROC analysis to detect delerium:

A cut off value for Jvo2 measured at day 3(Jvo2 3) of 53.5% (AUC=1,CI 95%,sensitivity 100%, specificity 100%,), and a cut off value for the PI at day 3 (PI3) of 1.2(AUC=0.88, CI 95%, 0.83-0.9, sensitivity 70%, specificity 100%).

DISCUSSION

A review of TCD studies of septic patients shows the reliance on cerebral vaso reactivity in response to acetazolamide administration [9, 10] or carbon dioxide [11, 12] and blood pressure [21] modifications, with conflicting results. Despite this, few studies calculated PI and RI as an estimate for measuring static VMCA along with gross estimation of cerebral blood flow.

In our study mean APACHE II was 29.2 and the mean ICU stay was 10.3 days. APACHE II score was higher in the delirium group than in non-delirium group (38 vs. 22.5 respectively) (p.value 0.00). Patients who developed delirium had significantly longer ICU LOS 13.9 day's vs7.8 days for non-delirium group with (*p*.value 0.00).

Rachid Attou et al included forty patients with sepsis in their study. In agreement to our study, they reported that Patients with higher PI (>1.3) were older (72 ± 13vs62 ± 16 years, p = 0.04). Those patients also reported higher APACHE II scores (23 ± 51vs 8 ± 5, p < 0.01) and had a longer ICU stay (11 days vs5 days p value =0.04). [20] However Charalampos Pierrakos et al concluded and statistically significant differences between septic and non-septic patients in terms of age (67 ± 11 vs. 67 ± 14 years, p = 0.99) or APACHE II score (21 ± 7 vs. 20 ± 5, p = 0.92).[21]Patrick Schramm et al studied thirty patients, five with severe sepsis and twenty-five with septic shock. According to their results, APACHE II score was 32 ± 6, with a mean age of 64 ± 17 years.[22].

We concluded that the main two causes of sepsis were pneumonia and urinary tract infections followed by skin & soft tissue infections and other sources (Abdominal, catheter related and sinusitis). Gram –ve organisms were the most prevalent in the studied population followed by gram +ve, fungal and anerobic organisms. Out of the 159 patients studied, 74 died during the ICU stay.

According to Rachid Attou, et al, the main source of infection was pulmonary infection in the majority of patients (64%). Gram-negative pathogens were responsible for sepsis in 46% of septic patients. The majority of patients (76%) presented a maximum PI > 1.1.[20]. On the contrary, Charalampos Pierrakos, et al reported that the main source of infection was pulmonary infection with one -or more- organ dysfunction. And 61% of these patients suffered from deterioration in consciousness level (GCS < 14).[21]

In our study we used the confusion assessment method CAM to assess the development of sepsis associated delirium, 91 patients developed delirium (57.2% Positive CAM ICU) while 68 patients did not develop delirium.

Leslie A. Wei, et al compared the evaluation method of CAM to a reference standard in seven high quality studies including 1071 patients collectively. The overall sensitivity was 94% (95% CI, 91–97%), and specificity was 89% (95% CI, 85–94%). CAM was adapted to be used in the ICU, ER, institutional settings, and for severity of delirium score. In applied studies, CAM-rated delirium is used as a risk factor as well as a reference standard.[23]

In the study of Rachid Attou, et al, twenty one patients suffered from delirium (55%) showing positive CAM-ICU test. Sixteen of them reported a positive CAM-ICU test on the first study day. Due to sedation, three other patients could not be evaluated on the first day, two of them were initially evaluated three days later and one was evaluated five days later. Two patients showed a negative CAM-ICU test on the first day but on the following day reported a positive test.[20]

According to Patrick Schramm, et al, an impaired AR was reported at the 1st day in most of the patients, followed by recovery during the following days. In 22 out of 29 patients SAD (CAM-ICU) was detected at day 4. The study also reported a weak correlation between the index of AR Mx and the inflammatory parameters - but with no markers of brain damage (NSE, S100). Patients with SAD reported an elevation in the marker S100. And the study concluded the absence of correlation in the diagnoses of delirium using CAM-ICU compared to EEG. As a result, the study recommended that impairment of AR and SAD is common in ICU patients, and impaired AR might be causative to trigger SAD.[22]

In our study MAP at the time of diagnosis was significantly lower in patients who developed delirium. Interestingly Sao2 was found higher in patients who developed delirium, however this was non-significant. There was no significant difference in JVO2 and Co2 levels as well.

Patrick Schramm, et al concluded that there is no correlation between SAD and cerebrovascular haemodynamic. This conclusion was based on studying patients with pathological EEG results and sepsis showing intact CO2 reactivity [24]. And by comparing the CBF autoregulation dependence on CO2 to dependence on blood pressure, the study reported that CO2 dependence is more resistant to influences.[22]

Charalampos Pierrakos et al reported higher arterial pCO2 in septic patients compared to the control group. In preserved vascular autoregulation, intense cerebral vasodilation is caused by acute hypercapnia. According to the study, high pCO2 isn't the main cause for the changes in vascular resistances that were observed in septic patients. Despite this, the study recommended that CO2 levels can affect cerebral autoregulation in septic shock patients. With more profound alterations in autoregulation detected in hypercapnic (pCO2 > 40 mmHg) compared to hypocapnic (pCO2 < 40 mmHg) patients [11]. No correlation was reported in the study between pCO2 levels and PI or RI.

Also no statistically significant difference was detected between septic patients and the control group in terms of CBF.[21]

In our study Transcranial Doppler findings in the study group who developed delirium had lower mean MCA velocity (VMCA) and higher pulsatility index at all times (significant P value 0.00). A positive correlation was observed between Jvo2 and VMCA on day 2 (r=0.8), and on day 3 (r=0.69). There was a negative correlation between PI and JVo2 on day 2(r= -0.5) and day 3(r=-o.57). Roc curve analyses the ability to detect delirium with a cut off value for Jvo2 measured at day 3(Jvo2 3) of 53.5% (sensitivity 100%, specificity 100%, P <0.05), and a cut off value for the PI at day 3 (PI3) of 1.2.(AUC= 0.88, CI 95%, 0.83-0.9 P <0.05vsensitivity 70%, specificity 100%).

In the Charalampos Pierrakos et al study, twenty-one patients (55%) check the number were found to suffer from confusion. The majority of the patients reported a PI > 1.1 (76%). PI on the first day(but not the third day) could predict a positive CAM-ICU test in septic patients (PI cut-off was 1.3, AUC was 0.905, $p < 0.01$, sensitivity was 95%, specificity was 88%, AUC was 0.618, and $p = 0.24$).Multivariable analysis in the study revealed a relation between PI on the first day and positive CAM-ICU test regardless of age and APACHE II score (OR: 5.6, 95% CI: 1.1-29, $p = 0.03$). The study also concluded that the group with initially high PI (>1.3) developed a decrease of the PI on the third day (1.81 ± 0.64 vs. 2.2 ± 0.71; $p = 0.02$). On the contrary, the other patients reported an increase in PI (1.01 ± 0.15 vs.1.58 ± 0.57; $p < 0.01$). Mean blood velocity in the middle cerebral artery and CBFi were found to be lower in patients with a high initial PI (36 ± 21 vs. 62 ± 28 cm/sec; $p < 0.01$, 328 ± 101 vs. 581 ± 108; $p < 0.01$, respectively) - but only on the 1st day.[21]

In the Charalampos Pierrakos et al, septic patients showed no statistically significant higher values of VmMCA (110 ± 34 cm/sec vs. 99 ± 28 cm/sec $p = 0.17$) or lower values of CBFi (497 ± 116 vs. 548 ± 110 $p = 0.06$). These patients also reported higher values of PI and RI (1.15 ± 0.25 vs. 0.98 ± 0.16 $p < 0.01$, 0.64 ± 0.08 vs. 0.59 ± 0.06 $p < 0.01$, respectively). [21]

The study of Szilárd Szatmári et al included 14 septic patients with disturbance of consciousness of any severity. The control group of the study was 20 non-septic persons without any previous diseases affecting cerebral vasore activity. Transcranial Doppler blood flow velocities were measured at rest and at 5, 10, 15 and 20 minutes after intravenous administration of 15 mg/kg acetazolamide. The study compared the two groups regarding the time course of the acetazolamide effect on cerebral blood flow velocity (cerebrovascular reactivity, CVR) and the maximal vasodilatory effect of acetazolemide (cerebrovascular reserve capacity, CRC).[25]

Ethical Approval

The study has been approved by the ethical committee of the University of Cairo and hence all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

CONCLUSION

TCD is an efficient and feasible exam to evaluate changes in cerebral perfusion during sepsis. We found that in delirium group VMCA was lower and PI higher at all times. There is a positive strong correlation between Jvo2 and VMCA on day 2 (r=0.8), and on day 3 (r=0.69) and a negative correlation between PI and JVo2 on day 2 (r=-0.5) and day 3 (r=-o.57). Hence changes in TCD findings and Jvo2 levels are associated with the development of delirium in septic patients.

Acknowledgements

The authors would like to thank the intensive care and radiology departments of the University of Cairo.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1]. Pytel P, Alexander J J. Pathogenesis of septic encephalopathy.Curr Opinoin Neurology. 2009; 22:283–287.

[2]. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett E. Pathophysiology of septic encephalopathy, a review. *Crit Care Med*. 2000; 28:3019–3024.

[3]. Nagaratnam N, Brakoulias V, Ng .Multiple cerebral infarcts following septic shock. *J ClinNeurosci*. 2002; 9:473–476.

[4]. Rosengarten B, Wolff S, Klatt S, Schermuly RT. Effects of inducible nitric oxide synthase inhibition or norepinephrine on the neurovascular coupling in an endotoxic rat shock model. *Crit Care*. 2009;3(4):R139.

[5]. Mihaylova S, Killian A, Mayer K, Pullamsetti SS, Schermuly R, Rosengarten B. Effects of anti-inflammatory vagus nerve stimulation on the cerebral microcirculation in endotoxinemic rats. *J Neuroinflammation.* 2012;3:183.

[6]. Sharshar T, Polito A, Checinski A, Stevens RD. Septic-associated encephalopathy–everything starts at a microlevel. *Crit Care*. 2010;3(5):199.

[7]. Bowton DL, Bertels NH, Prough DS, Stump DA. Cerebral blood flow is reduced in patients with

sepsis syndrome. *Crit Care Med*. 1989;3(5):399–403
[8]. Sharshar T, Carlier R,et al.. Brain lesions in septic shock: a magnetic resonance imaging study. *Intensive Care Med*. 2007;3(5):798–806
[9]. Fülesdi B, Szatmári S, et al. Cerebral vasoreactivity to acetazolamide is not impaired in patients with severe sepsis. *J Crit Care*. 2012;3(4):337–343.
[10]. Szatmári S, Végh T, Csomós A, Hallay J, Takács I, Molnár C, Fülesdi B. Impaired cerebrovascular reactivity in sepsis-associated encephalopathy studied by acetazolamide test. *Crit Care.* 2010;3(2):R50.
[11]. Bowie RA, O'Connor PJ, Mahajan RP. Cerebrovascular reactivity to carbon dioxide in sepsis syndrome.Anaesthesia. 2003;3(3):261–265.
[12]. Matta BF, Stow PJ. Sepsis-induced vasoparalysis does not involve the cerebral vasculature: indirect evidence from autoregulation and carbon dioxide reactivity studies. *Br J Anaesth*. 1996;3(6):790–794.
[13]. Taccone FS, Castanares-Zapatero D, Peres-Bota D, Vincent JL, Berre' J, Melot C. Cerebral autoregulation is influenced by carbon dioxide levels in patients with septic shock. *Neurocrit Care.* 2010;3(1):35–42.
[14]. Rosengarten B, Krekel D, Kuhnert S, Schulz R. Early neurovascular uncoupling in the brain during community acquired pneumonia*. Crit Care*. 2012;3(2):R64.
[15]. Szatmári S, Végh T, Csomós A, Hallay J, Takács I, Molnár C, Fülesdi B. Impaired cerebrovascular reactivity in sepsis-associated encephalopathy studied by acetazolamide test. *Crit Care*. 2010;14:R50.
[16]. Pierrakos C, Antoine A, Velissaris D, Michaux I, Bulpa P, Evrard P, Ossemann M, Dive A. Transcranial doppler assessment of cerebral perfusion in critically ill septic patients: a pilot study. *Ann Intensive Care*. 2013;3:28.
[17]. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee Including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
[18]. Gosling RG, King DH: Arterial assessment by Doppler-shift ultrasound. *Proc R Soc Med*. 1974, 67: 447-449.
[19]. Wei LA, Fearing MA, Sternberg EJ, Inouye SK: The confusion assessment method: a systematic review of current usage. *J Am Geriatr Soc*. 2008, 56: 823-830.
[20]. Charalampos Pierrakos, RachidAttou, Laurence Decorte, Athanasios Kolyviras, Stefano Malinverni, Philippe Gottignies, Jacques Devriendt, and David De Bels. Transcranial Doppler to assess sepsis-associated encephalopathy in critically ill patients .*BMC Anesthesiol*.2014; 14: 45.
[21]. Charalampos Pierrakos, Aurélie Antoine, Dimitrios Velissaris, Isabelle Michaux,1 Pierre Bulpa, Patrick Evrard, Michel Ossemann, and Alain Dive. Transcranial doppler assessment of cerebral perfusion in critically ill septic patients: a pilot study. *Ann Intensive Care*. 2013; 3: 28.
[22]. Patrick Schramm, Klaus Ulrich Klein, Lena Falkenberg, Manfred Berres,2 Dorothea Closhen, Konrad J Werhahn, Matthias David, Christian Werner, and Kristin Engelhard.Impaired cerebrovascular autoregulation in patients with severe sepsis and sepsis-associated delirium.Crit Care. 2012; 16(5): R181.
[23]. Sateesh Pujari, & Estari Mamidala. (2015). Anti-diabetic activity of Physagulin-F isolated from Physalis angulata fruits. The American Journal of Science and Medical Research, 1(2), 53–60. https://doi.org/10.5281/zenodo.7352308
[24]. Leslie A. Wei, B.A., Michael A. Fearing, Ph.D., Eliezer J. Sternberg, and Sharon K. Inouye, M.D., MPH The Confusion Assessment Method (CAM): A Systematic Review of Current Usage. J Am Geriatr Soc. 2008 May; 56(5): 823–830.
[25]. Thees C, Kaiser M, Scholz M, Semmler A, Heneka MT, Baumgarten G, Hoeft A, Putensen C. Cerebral haemodynamics and carbon dioxide reactivity during sepsis syndrome. Crit Care. 2007;16:R123.
[26]. Szilárd Szatmári, Tamás Végh, Ákos Csomós, Judit Hallay, István Takács, Csilla Molnár, and Béla Fülesdi. Impaired cerebrovascular reactivity in sepsis-associated encephalopathy studied by acetazolamide test. Crit Care. 2010; 14(2): R50.